PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 73.WO1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2004/043609	International filing date *(day/month/year)* 22.12.2004	Priority date *(day/month/year)* 23.12.2003
International Patent Classification (IPC) or national classification and IPC INV. C07D471/10 A61K31/40 A61K31/47 A61P9/00 A61P25/00 C07D471/00		
Applicant ARENA PHARMACEUTICALS, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20.07.2005	11.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bakboord, J Telephone No. +49 89 2399-

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043609

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-177 as originally filed

   Claims, Numbers

   1-81 as originally filed

   Drawings, Sheets

   1/6-6/6 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043609

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 19-53, 79

because:

☒ the said international application, or the said claims Nos. 19-53, 59-64, 78, 79 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 65-77, 80, 81

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6, 7, 9, 10, 14, 19-64, 78, 79
	No:	Claims	1-5, 8, 11, 13, 15-18
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-64, 78, 79
Industrial applicability (IA)	Yes:	Claims	1-18, 54-58
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2004/043609

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 19-53, 59-64, 78, 79 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

The present claims contain so many options and possible variations that a lack of clarity an conciseness within the meaning of Art 6 PCT and sufficiency of disclosure within the meaning of Art 5 PCT arises to such an extent as to render a meaningful search of the whole of the breath of the claims impossible. Consequently the search has been carried out for those parts of the application only which do appear to be clear and concise and for which pharmaceutical data are available, namely the compounds of formula I in which A = B = CH_2CH_2, W=X=Y=Z is CH, o = 0, G is C(=O)Ar or $S(=O)_2$Ar, Ar is phenyl, naphthyl, pyridyl, fluorene, adamantane, thiophene, E-R_1 is CH_2-cyclopropyl, CH_2-CH=CH_2 or piperidinyl. This written opinion is therefore based on these compounds only.

No search was carried out for claims 65-77 and 80, 81 because said claims are considered as reach-through claims. The claims encompass compounds defined only by their desired function, contrary to the requirements of clarity of Art 6 PCT, because the result to be achieved type of definition does not allow the scope of the claim to be ascertained. The fact that any compound could be screened does not overcome this objection, as the skilled person would not have knowledge beforehand as to whether it would fall within the scope claimed. Undue experimentation would be required to screen compounds randomly. This non-compliance with the substantive provisions is to such an extent, that a meaningful search of said claims was not possible.

IV Lack of unity of invention

As has already been acknowledged in the description, the Mas receptor is known. The problem to be solved in claims 1-58 and 79 may therefore be regarded as the

provision of compounds which act as inverse agonists of the Mas receptor. The problem to be solved in claims 59-78, 80 and 81 may be regarded as a method for identifying compounds which act as agonists of the Mas receptor. No unifying technical relationship amongst these independently differentiating problems is present. Therefore it is considered that the application lacks unity of invention (Art 13 PCT) and that the subjects listed above can be distinguished.

V Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.1 The present invention relates to spiroindoline compounds useful as cardio-protective or neuro-protective agents in mammals.

V.2 Reference is made to the following documents:

D1: WO 01/12630 A (SEPRACOR INC) 22 February 2001 (2001-02-22)
D2: DATABASE CHEMCAT Chemical Abstracts; 444054-63-1(RN) 1 January 2004 (2004-01-01), XP002335475
D3: WO 02/16432
D4: WO 03/039434

V.3 Document D1 discloses benzazepine piperidine & spiroquinoline piperidine derivatives as ligands for mammalian G-protein coupled receptors (see the examples).
Document D2 discloses spiroindoline compounds corresponding to compounds exemplified in the present application (see entry no. 9, 13, 15,16, 18, 20, 21 and 23). The publication of the chemical library is 01.01.2004, which is after the priority date. The registry numbers where first entered on 16.08.2002. Therefore it is considered that they prejudice the novelty of compounds of formula I.
Document D3 discloses a method for screening for ligands of the MAS receptor; i.e. agonists or antagonists, the method comprising incubating (contacting) a MAS receptor with a substance suspected to be an agonist or antagonist by detecting any effect of binding (see claims 49-51 and 53). D3 does, however, not specifically

disclose the identification of a cardio-protective compound.
Document D4 discloses the use of MAS-receptor antagonists in the treatment of cardiovascular diseases (see claims 24-26).

A compound of formula I as described in claims 1-5, 8, 11-13 is disclosed in document D2. Claims 1-5, 8, 11-13 therefore do not fulfill the requirements of Art 33(2) PCT.

A compound of formula I as described in claims 6, 7, 9, 10, 14 is disclosed in none of the documents. Claims 6, 7, 9, 10, 14 therefore fulfill the requirements of Art 33(2) PCT.

A compound of formula I, which is cardio-protective, does not significantly increase blood pressure and is neuro protective is disclosed in document D2 (entries nr 9, 18). Claims 15-17 therefore do not fulfill the requirements of Art 33(2) PCT.

A compound of formula I for use in a method of treatment is disclosed in document D2 (entries 9, 18). Claim 18 therefore does not fulfill the requirements of Art 33(2) PCT.

A method for treating or preventing a vascular or cardiovascular disease or disorder, comprising administering a compound of formula I to a patient is disclosed in none of the documents. Claims 19-33 therefore fulfill the requirements of Art 33(2) PCT.

A method for treating or preventing a neurological disease or disorder, comprising administering a compound of formula I to a patient is disclosed in none of the documents. Claims 34-46 therefore fulfill the requirements of Art 33(2) PCT.

A method for treating or preventing a disorder treatable or preventable by inhibiting Mas receptor function, comprising administering a compound of formula I to a patient is disclosed in none of the documents. Claims 47-52 therefore fulfill the requirements of Art 33(2) PCT.

A method for inhibiting Mas receptor function in a cell comprising contacting a cell capable of expressing the Mas receptor with a compound of formula I is disclosed in none of the documents. Claim 53 therefore fulfills the requirements of Art 33(2) PCT.

A pharmaceutical composition comprising a compound of formula I is disclosed in none of the documents. Claim 54 therefore fulfills the requirements of Art 33(2) PCT.

A method for the manufacture of a medicament comprising a compound of formula I is disclosed in none of the documents. Claims 55-58 therefore fulfill the requirements of Art 33(2) PCT.

A method for identifying a cardio-protective compound comprising contacting a candidate compound with a MAS receptor is disclosed in none of the documents. Claims 59-64 therefore fulfill the requirements of Art 33(2) PCT.

A method for selectively inhibiting MAS receptor activity in a human host comprising administering a compound that selectively inhibits activity of the MAS receptor is disclosed in none of the documents. Claim 78 therefore fulfills the requirements of Art 33(2) PCT.

A method for selectively inhibiting Mas receptor activity in a human host, comprising administering a compound of formula I is disclosed in none of the documents. Claim 79 therefore fulfills the requirements of Art 33(2) PCT.

V.4 Inventive step

V.4.1 Starting from document D1 the problem to be solved in claims 1-58 and 79 may be regarded as how to provide novel possibly improved compounds which act as inverse agonists of the MAS receptor. The solution of the applicant resides in providing spiroindoline piperidine compounds, substituted at the nitrogen atom of the indoline group with a group C(=O)Ar or $S(=O)_2Ar$. The applicant shows in table 3 that certain compounds of the invention are MAS receptor inverse agonists. As the compounds of the present application have not been made obvious by the prior art the solution in as far as novel may be regarded as

inventive see however point V.4.2.

V.4.2 The scope of the claims is too broad. Examples are given only for compounds of formula I in which A = B = CH_2CH_2, W=X=Y=Z is CH, o = 0, G is C(=O)Ar or $S(=O)_2Ar$, Ar is phenyl, naphthyl, pyridyl, fluorene, adamantane, thiophene, E-R_1 is CH_2-cyclopropyl, CH_2-CH=CH_2 or piperidinyl. All the other variations seem to comprise possibilities not yet explored by the applicant which might not solve the technical problem. Therefore inventive step can at present not be acknowledged (Art 33(3) PCT) for claims 1-58 and 79.

V.4.3 The problem to be solved in claims 59-64 and 78 may be regarded as a method for identifying a cardio-protective compound. The solution of the applicant resides in contacting a candidate compound with a MAS receptor and determining whether the receptor functionality is decreased. If so the candidate compound is considered to be cardio-protective. As it was known from document D4 that MAS receptor antagonists as well as agonists are useful for treating cardiovascular diseases it was obvious for a person skilled in the art to utilize the screening method disclosed in document D3 for identifying further compounds useful to treat cardiovascular diseases. Based on both documents it was also not surprising or unexpected that easily identifiable MAS receptor antagonists are suitable to selectively inhibit MAS-receptor activity in a human host.
Following the above reasoning claims 59-64 and 78 are considered not to involve an inventive step.

V.5 Industrial applicability

For the assessment of the present claims 19-53, 59-64, 78, 79 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical

treatment.

VI Certain documents cited

DATABASE CHEMCAT Chemical Abstracts; 444054-63-1(RN) 1 January 2004 (2004-01-01), XP002335475